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(19)

(54) SUBSTITUTED METHOXYAMINE DERIVATIVES

(71) We, GYOGYSZERKUTATO INTEZET, of Szabadsagharcosok utja 47—49, Budapest IV, Hungary, a Hungarian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new process for the preparation of substituted methoxyamine derivatives. The invention also relates to certain novel substituted methoxyamine compounds.

There have already been described some methods in the literature according to which O-substituted hydroxylamine compounds (also referred to as substituted methoxyamine derivatives) can be prepared from hydroxylamines having a protecting group attached to the nitrogen atom.

According to one of these known processes (Chem. Ber. *16*, 175/18831) acetonoxima is reacted in ethanol with benzylchloride in the presence of sodium ethylate, and the obtained crude O - benzyl - acetonoxime is boiled in aqueous hydrochloric acid to give benzyloxyamine or its hydrochloride.

According to another known process J. Chem. Soc. *1930*, 226) benzhydroxamic acid is converted into its allyl ether with allyl bromide in alcoholic potassium hydroxide solution, and the obtained ether is debenzoylated in acidic or alkaline medium to yield allyloxyamine.

According to a third known method (Helv. Chim. Acta *45*, 1381/1962/) N - hydroxy - urethane is reacted in ethanolic medium with benzyl chloride in the presence of sodium ethylate, and the obtained N - benzyloxy - urethane is boiled in an alcoholic potassium hydroxide solution to yield benzyloxamine.

According to another known method (Brit. Pat. No. 983,664) N - hydroxy - phthalimide is reacted with 4 - methoxybenzylchloride in dimethylformamide medium, in the presence of triethylamine, and the obtained N - (4 - methoxybenzyolxy) - phthalamide is convented into 4 - methoxy - benzyloxamine via hydrazinolysis.

A common feature of the above-mentioned methods is that the corresponding derivatives of hydroxylamine having a protecting group attached to the nitrogen atom (acetonoxime, benzhydroxamic acid, N - hydroxy - urethane, or N - hydroxyphthalimide, respectively) are substituted on the oxygen atom using a halogenated compound, and the protecting group (isopropylidene group, α - hydroxybenzylidene group, carbethoxy group or phthaloyl respectively) of the obtained intermediates is split off.

The disadvantages of the known methods are the following: According to the first, second and third known methods, a reactive halogenated compound is reacted with the appropriate hydroxyamine derivative having a protecting group attached to the nitrogen atom (namely with acetonoxime, benzhydroxamic acid, and N - hydroxy - urethane, respectively) in ethanolic medium, in the presence of sodium or potassium ethylate. Under the conditions of these reactions a part of the halogenated compound suffers solvolysis, i.e., it enters into reaction with ethanol. Accordingly, a part of the reagent is consumed as a consequence of by-product formation, further the pH of the reaction mixture decreases due to the solvolysis, causing a decrease of the reaction rate. A further disadvantage is that the intermediates obtained according to the first two methods (O-substituted acetonoximes and O-substituted hydroxamic acids, respectively)

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generally have low melting points, and their isolation in pure state is difficult and runs with low or medium yields. For this reason, the intermediates obtained in the first two methods are generally introduced into the hydrolysis step without isolation and purification, thus the end-products, i.e. the substituted methoxyamine compounds, can only be isolated from the various contaminations with great difficulties.

A further common disadvantage of the first two methods resides in that if they are used for the preparation of substituted methoxyamines having higher molecular weight and more complicated structure, halogenated compounds of complicated structure are to be used which, in turn, either cannot be crystallized or distilled due to their instability, or their purification runs with high losses. For this reason the halogenated compounds are to be used in crude state, and under these conditions it is essential that the first step of the synthesis, i.e. the reaction of the halogenated compound with acetonoxime or with benzhydroxamic acid, respectively, takes place readily and with high yields, and results in the formation of readily isolable, pure intermediates. As it has been pointed out in the foregoing, however, the isolation of the intermediates is generally difficult, and thus this step of the synthesis runs generally with low or medium yields. A further common disadvantage of the first three methods is that they either cannot be realized for the preparation of subsituted methoxyamines containing groups sensitive to acids or alkaline agents (e.g. ester or amide groups), or such compounds can only be prepared with medium or low yields. This can be explained by the fact that the acidic or alkaline hydrolysis of the intermediates (O-substituted acetonoximes, O-substituted benzhydroxamic acids or O-substituted N-hydroxy-urethanes, respectively) require severe conditions, and under these conditions the sensitive groups are partially or totally decomposed. Accordingly, the aimed products can only be prepared with low yields, or they cannot be isolated at all. Moreover, according to the literature (Zh. Org. Khim. *3*, 1207/1967/) the methoxyamine end products decompose on action of strong acidic or alkaline media, which results in a further lowering of the yield.

On the other hand, according to the fourth known method, the N - (substituted methoxy) - phthalimide intermediates can be prepared with high yields by reacting the N-protected hydroxylamine derivative (i.e. N - hydroxy - phthalimide) with the appropriate halogenated compounds. The disadvantage of this method is, however, that the N - (substituted methoxy) - phthalimides can be converted into the desired substituted methoxyamines by removing the phthaloyl group. The latter group can be removed by hydrazinolysis, which reaction, in turn, can only be carried out with great difficulties. A further disadvantage of this method is that the yield of the reaction varies considerably with the nature of the substituted methoxy group, the reaction cannot be reproduced with identical results, and when the process is carried out in larger scale—even in batches of about 50 to 100 g.—, the yields are considerably lower due to side-reactions (e.g. dimerization). Moreover, if N - (substitued methoxy) - phthalimides containing hydrazine-reactive groups (e.g. ester radicals or halogens) are subjected to hydrazinolysis, these reactive groups enter into undesirable side-reactions with hydrazine hydrate. A further disadvantage is that phthalic hydrazide, which is always formed in the dephthaloylation step, partially dissolves in the alcohols used as reaction medium, and the presence of phthalic hydrazine renders the isolation of the end-products more difficult. Some disadvantages arise also from the use of hydrazine hydrate. As the preparation of anhydrous hydrazine is accompanied by risk of explosion, this substance should be replaced in the reactions by hydrazine hydrate. The separation of the pure hydrazine hydrate (corresponding to the formula

$$N_2H_4 . H_2O)$$

from water is very difficult, since the boiling points of these substances are almost the same; accordingly, in practice, hydrazine hydrate is used in the form of a 75 to 80% aqueous solution. Using this reagent, however, water is inevitably introduced into the reaction mixture, which causes a further difficulty in the isolation of the end-products in the form of their salts, because the solubility of these salts considerably increases in the presence of water.

The present invention aims at ensuring a new process for the preparation of various types of substituted methoxyamines having increasing pharmaceutical importance (Arch. Pharmacodyn. *166*, 305/1967/; Science *154*, 1017/1966/), which process can also be carried out in industrial scale and provides the aimed products with higher yields than the known ones.

We have found that substituted methoxyamines of the general formula

$$R^1CH(R^2)ONH_2$$

wherein R^1 represents an aliphatic, aromatic or heterocyclic radical and R^2 is a hydrogen atom or a saturated or unsaturated, straight-chained or branched C_{1-4} alkyl group, can be prepared with high yields and high purity in a very advantageous, safe and

readily conductable process by reacting the appropriate N - (substituted methoxy) - phthalimides with certain bases.

This discovery is very surprising for the following reasons: It is known that N - (substitued methoxy) - phthalimides—besides the above-mentioned hydrazinolysis—can only be dephthaloylated on action of strong acidic or alkaline media. Dephthaloylation in acidic medium, however, runs with low yields even in the case of N - alkoxy - phthalimides having very simple structure, e.g. N - methoxy- or N - ethoxy - phthalimide (J. Org. Chem. *30*, 1270/1965/), and benzyloxyamines can even be debenzylated in acidic media (J. Chem. Soc. *1960*, 229). In alkaline medium and at atmospheric pressure one of the amide bonds of the phthaloyl ring instantaneously splits off and O-substitued phthal - monohydroxamic acid derivatives are formed; the splitting of the other amide-bond, however, can only be carried out under elevated pressures. As it is known from the literature (Zh. Org. Khim. 3, 1207/1967/), alkoxyamines decompose when heated in alkaline medium.

Thus it is very surprising and could not be foreseen on the basis of the technical literature that N - (substituted methoxy) - phthalimides can be dephthaloylated with certain amines even under very mild condition, and thus the substituted methoxyamines can be prepared with excellent yields.

Thus, the invention consists in a process for the preparation of substituted methoxyamines of general formula:

$$R^1CH(R^2)ONH_2$$

or salts thereof, in which R^1 is an aliphatic, aromatic or heterocyclic radical and R^2 is a hydrogen atom or a saturated or unsaturated straight-chain or branched C_{1-4} alkyl group, by reacting an N - (substitued methoxy) - phthalamide of general formula:

$$R^1CH(R^2)ON=A$$

in which A is a substituted or unsubstituted phthaloyl group and R^1 and R^2 have the same meanings as above, with an amine of general formula R^3NH_2 or with a salt thereof, in which R^3 is a hydrogen atom or an aliphatic, aromatic, araliphatic, alicyclic or heterocyclic radical, and optionally reacting the obtained base with an acid to produce a salt or reacting the obtained salt with a strong base to produce the free base.

In a preferred embodiment of the invention, the N - (substitued methoxy) - phthalimide is heated with an equimolar quantity of an aliphatic amine, preferably a lower aliphatic amine, e.g. allylamine or n-butylamine, after which an inorganic or organic acid, e.g. hydrochloric, hydrobromic, sulphuric, tartaric, maleic or fumaric acid, is added to the reaction mixture, and the corresponding salt of the substituted methoxyamine is isolated. The salt can be transformed into the free base by reacting with a strong base.

In a further preferred embodiment of the invention, the reaction of the N - substituted methoxy) - phthalimide with the amine is carried out in the absence of any solvent, said N - (substituted methoxy) - phthalimide and said amine being fused together at the boiling point of said amine.

If a solvent is used for the reaction between the N - (substituted methoxy) - phthalimide and the primary amine, it is preferably an alcohol having from 1 to 3 carbon atoms and the reaction is preferably carried out at the boiling point of the solvent.

According to a further preferred method of the invention the reaction is carried out using n-butyl-, allyl-, cyclopropyl-, or cyclohexylamine or aniline.

Those compounds of the general formula

$$R^1CH(R^2)ONH_2$$

wherein R^1 represents a prop - 1 - enyl, 4 - n - octyloxy - 3,5 - dimethoxyphenyl or 3 - pyridylmethyl group, are new substances. The N - (substituted methoxy) - phthalimides used as starting substances in the preparation of the above compounds are also new, and can be prepared by methods known per se (Chimia 18, *1*/1964/).

The primary amine reactants used in the process of the invention are selected by taking into consideration the following points:

If the primary amine is used in equimolar amount in the reaction of N - (substituted methoxy) - phthalimides and primary amines, at N - substituted phthalimide by-product is formed besides the substituted methoxyamine end-products, while if molar excess or higher amounts of the primary amine are used, a N,N′ - disubstitued - phthalic acid diamide by-product is formed. Accordingly, the primary amine is selected so as to give an N-subsituted phthalimide or N,N′-disubstituted phthalic acid diamine which can easily be separated from the obtained substituted methoxyamine end-product. Thus, for example, if the substituted methoxyamine end-product is insoluble in the reaction medium (e.g. in an alcohol), the primary amine is selected so as to give an N-substitued phthalimide or N,N′-disubstitued phthalic acid diamide highly soluble in the same medium. In this case the substituted methoxyamine can readily be isolated by filtration. In turn, if the substituted methoxyamine end-product dissolves well in the reaction medium, the primary amine is selected so as to give an N-substituted

phthalimide or N,N' - disubstitued phthalic acid diamide practically insoluble in the same solvent. In this case the reaction mixture is filtered, and the desired alkoxyamine compound is isolated from the filtrate by evaporation or by precipitation in the form of its salt.

Preferably the following mineral or organic acids are used for salt-formation: hydrochloric or sulphuric acid in ethanol or isopropanol solution, or fumaric, maleic, tartaric, citric, mandelic acids in ethanolic, isopropanolic, or acetonic solution.

The advantages of the new process according to the invention as compared to the known ones are the following:

a) the reaction is simple and unidirectional;

b) the reaction can easily be monitored by chromatography, and thus the end-point can readily be observed;

c) the yield of the reaction is high even if batches of some kg. are worked up, and the quality of the end-product is excellent;

d) the primary amines can be selected from a wide range; accordingly if the N - (substituted methoxy) - phthalimide contains groups sensitive to the raction of strongly alkaline amines (e.g. ester groups or halogens), the reaction can also be carried out using amines having lower reactivity against these groups (such compounds are e.g. the aromatic amines).

The invention is further illustrated by the following Examples:

Example 1

Preparation of allyloxyamine

A mixture of 10.16 g. of N - (allyloxy) - phthalimide, 30 ml. of alcohol and 3.7 g. of n-butylamine is boiled for 20 minutes. The solution is allowed to cool, thereafter it is acidified with alcoholic hydrochloric acid to Kongo blue, and the allyloxyamine hydrochloride is precipitated with 150 ml. of ether. The separated precipitate is filtered off, washed several times with ether and dried. 4.65 g. (84.5%) of allyloxyamine hydrochloride are obtained; m.p.: 175—176°C.

Example 2

Preparation of crotyloxyamine

Step "A":

A mixture of 6.5 g. of triethylamine and 10 ml. of dimethylformamide is added dropwise, under stirring and ice-cooling to a mixture of 10.5 g. of N - hydroxy - phthalimide, 8.5 g. of crotylbromide and 50 ml. of dimethylformamide. The reaction mixture is stirred in ice-bath for a further hour, thereafter it is allowed to stand for 2 days. The crystal suspension is poured into 100 ml. of 5% aqueous hydrochloric acid, the separated precipitate is filtered off, dried and crystallized from alcohol. 11.8 g. (84.5%) of N - crotyloxy - phthalimide are obtained; m.p.: 97—100°C.

Step "B":

2.17 g. of the above product are dissolved in 45 ml. of methanol, and a solution of 0.87 g. of n-amylamine in 5 ml. of methanol are added dropwise to this solution at 10°C. The reaction mixture is allowed to stand at room temperature. Next day the solvent is evaporated, the residue is dissolved in 10 ml. of alcohol, and 2.5 ml. of 20% alcoholic sulphuric acid are added to the solution. 2.95 g. (87%) of di-crotyloxyamine sulphate are obtained; m.p.: 160—164°C (under decomposition).

Example 3

Preparation of n-hexyloxyamine

A mixture of 2.47 g. of N - hexyloxy - phthalimide, 50 ml. of alcohol and 1.98 g. of cyclohexylamine is boiled for 20 minutes. The mixture is allowed to cool, the separated N,N' - dicyclohexyl - phthalimide (3.1 g./94.5%/, m.p.: 253—254°C) is filtered off, and the filtrate is evaporated. The residue is dissolved in 30 ml. of ether, the solution is acidified to Kongo-blue with alcoholic hydrochloric acid, the separated precipitate is filtered off, washed several times with ether and dried. 1.2 g. (78%) of n-hexyloxyamine hydrochloride are obtained; m.p.: 151—152°C.

Example 4

Preparation of n-hexadocycloxyamine

3.87 g. of N - (n - hexadecyloxy) - phthalimide are reacted as described in Example 3 to give 2.3 g. (81%) of n-hexadecyloxyamine hydrochloride; m.p.: 133—134°C.

Example 5

Preparation of benzyloxyamine

Method 1)

2.53 g. of N - benzyloxy - phthalimide are reacted as described in Example 2, step "B" to yield 1.44 g. of benzyloxyamine hydrochloride; m.p.: 234—236°C.

Method 2)

A mixture of 2.53 g. of N - benzyloxy - phthalimide, 45 ml. of methanol and 0.93 g. of aniline is boiled for 4 hours, thereafter it is evaporated in vacuo. The solid residue is triturated in a mixture of 20 ml. of ether and 5 ml. of alcohol. 1.7 g. (76.5%) of N - phenyl - phthalimide are obtained as insoluble solid residue, m.p.: 202—204°C. The mother liquor is mixed with 10 ml. of 17% alcoholic hydrochloric acid, and benzyloxyamine hydrochloride is precipitated with 20 ml. of ether. 1.1 g. (70.0%) of benzyloxyamine hydrochloride are obtained; m.p. 232—235°C.

Example 6

Preparation of 4-methoxy-benzyloxyamine

2.83 g. N - (4 - methoxy - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 1.66 g. (88%) of 4 - methoxy - benzyloxyamine hydrochloride; m.p.: 214—216°C (under decomposition).

Example 7

Preparation of 3-nitro-benzyloxyamine

2.98 g. of N - (3 - nitro - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 1.7 g. (83.5%) of 3 - nitro - benzyloxyamine hydrochloride; m.p.: 168—171°C.

Example 8

Preparation of 4-nitro-benzyloxyamine

Method 1)

2.98 g. N - (4 - nitro - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 1.8 g. (88%) of 4 - nitro - benzyloxyamine hydrochloride; m.p.: 197—199°C.

Method 2)

A mixture of 2.98 g. of N - (4 - nitro - benzyloxy) - phthalimide, 10 ml. of alcohol and 0.48 g. of allylamine is boiled for 20 minutes. The mixture is allowed to cool, thereafter the solution is acidified to Kongo-blue with alcoholic hydrochloric acid, and 50 ml. of ether are added to the acidic mixture. The separated precipitate is filtered off, washed several times with ether and dried. 1.6 g. (78.5%) of 4-nitro-benzyloxy-amine hydrochloride are obtained, m.p.: 197—198°C.

Method 3)

A solution of 5.96 g. of N - (4 nitro - benzyloxy) - phthalimide in 150 ml. of 5% aqueous-alcoholic ammonium hydroxide is stirred for 6 hours at room temperature, then it is left to stand. Next day the mixture is acidified to Kongo-blue with aqueous hydrochloric acid, the separated precipitate is filtered off and dried. 3.1 g. (95.5%) of phthalic acid diamide are obtained. The filtrate is rendered alkaline with 20% sodium-hydroxide solution, extracted with 5×70 ml. of ether, and the combined ethereal solution is dried over potassium carbonate. The drying agent is filtered off, the filtrate is acidified to Kongo-blue with alcoholic hydrochloric acid, the separated precipitate is filtered off, washed with ether and dried. 3.3 g. (81.5%) of 4 - nitro - benzyloxy-amine hydrochloride are obtained, m.p.: 194—196°C.

Method 4)

A mixture of 2.98 g. of N - (4 - nitro - benzyloxy) - phthalimide, 80 ml. of alcohol and 15.2 ml. of alcoholic butylamine acetate is boiled for 3 hours, thereafter the mixture is evaporated in vacuo. The residue is stirred with 5% aqueous hydrochloric acid, and the acidic mixture is extracted with 3×50 ml. of chloroform. The chloroform solutions are combined, dried over magnesium sulphate, the drying agent is filtered off, and the filtrate is evaporated in vacuo. The residue is fractionally distilled ni vacuo. 1.56 g. (78%) of N - butyl - phthalimide are obtained, b.p.: 125—130°C/2 mm Hg.

The acidic solution is saturated with potassium carbonate, extracted with 3×50 ml. of chloroform, and the chloroform solution is dried over potassium carbonate. The drying agent is filtered off, the filtrate is acidified to Kongo-blue with alcoholic hydrochloric acid, and the separated precipitate is filtered off. 1.32 g. (66%) of 4 - nitro - benzyloxyamine hydrochloride are obtained.

Example 9

Preparation of 3-methoxy-benzyloxyamine

A mixture of 2.83 g. of N - (3 - methoxy - benzyloxy) - phthalimide, 50 ml. of alcohol and 2.14 g. of benzylamine is boiled for 20 minutes. The mixture is allowed to cool, the separated N,N - dibenzyl - phthalamide is filtered off and dried. 1.6 g. (84%) of N,N - dibenzyl - phthalamide are obtained. The alcoholic filtrate is acidified to Kongo-blue with alcoholic hydrochloric acid, and the end-product is precipitated with ether. 1.8 g. (81%) of 3 - methoxy - benzyloxyamine hydrochloride are obtained; m.p.: 123—125°C.

Example 10

Preparation of 4-chloro-benzyloxyamine

2.88 g. of N - (4 - chloro - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 1.7 g. (87.5%) of 4 - chloro - benzyloxyamine hydrochloride; m.p.: 242—243°C.

Example 11

Preparation of 4-methyl-benzyloxyamine

2.65 g. of N - (4 - methyl - benzyloxy) - phthalimide are reacted as described in Example 5, method 2) to yield 1.52 g. (88.5%) of 4 - methyl - benzyloxyamine hydrochloride; m.p.: 233—234°C.

Example 12

Preparation of 2-chloro-benzyloxyamine

2.87 g. of N - (2 - chloro - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 1.7 g. (88%) of 2 - chloro - benzyloxyamine hydrochloride; m.p.: 242—243°C.

Example 13

Preparation of 1-(3-nitro-phenyl)-ethyloxy-amine

3.1 g. of N - [1 - (3 - nitro - phenyl) - ethoxy] - phthalimide are reacted as des-

cribed in Example 1 to yield 1.15 g. (63%) of 1 - (3 - nitro - phenyl) - ethoxyamine hydrochloride; m.p.: 109—112°C.

Example 14

Preparation of 3-nitro-4-hydroxy-benzyloxy-amine

3.14 g. of N - (3 - nitro - 4 - hydroxy - benzyloxy) - phthalimide are reacted as described in Example 9 to yield 1.83 g. (83%) of 3 - nitro - 4 - hydroxy - benzyloxyamine hydrochloride; m.p.: 184—187°C.

Example 15

Preparation of 3-nitro-4-chloro-benzyloxy-amine

3.3 g. of N - (3 - nitro - 4 - chloro - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 2.2 g. (94.8%) of 3 - nitro - 4 - chloro - benzyloxyamine hydrochloride; m.p.: 172—175°C.

Example 16

Preparation of 3-nitro-4-bromo-benzyloxy-amine

3.77 g. of N - (3 - nitro - 4 - bromo - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 2.8 g. (81%) of 3 - nitro - 4 - bromo - benzyloxyamine hydrochloride; m.p.: 179—182°C.

Example 17

Preparation of 3-nitro-4-methoxy-benzyloxy-amine

A mixture of 3.24 g. of N - (3 - nitro - 4 - methoxy - benzyloxy) - phthalimide, 0.94 g. of 2 - amino - pyridine and 50 ml. of alcohol is boiled for one hour, thereafter the mixture is evaporated in vacuo. The residue is stirred with 4% aqueous hydrochloric acid and extracted wtih 3×50 ml. of chloroform. The aqueous acidic solution is saturated with potassium carbonate, extracted with 3×50 ml. of chloroform, and the chloroform solution is dried over potassium carbonate. The drying agent is filtered off and the filtrate is acidified to Kongo-blue with alcoholic hydrochloric acid. The separated precipitate is filtered off, washed with chloroform and dried. 1.78 g. (76%) of 3 - nitro - 4 - methoxy - benzyloxyamine hydrochloride are obtained; m.p.: 169—172°C.

Example 18

Preparation of 2,6-dichloro-benzyloxy-amine

5.5 g. N - (2,6 - dichloro - benzyloxy) - phthalimide are reacted as described in Example 17 to yield 3.55 g. (91%) of 2,6 - dichloro - benzyloxyamine hydrochloride; m.p.: 199—201°C.

Example 19

Preparation of 3-hydroxy-4-nitro-benzyloxy-amine

3.14 g. of N - (3 - hydroxy - 4 - nitro - benzyloxy) - phthalimide are reacted as described in Example 1 to yield 1.87 g. (85%) of 3 - hydroxy - 4 - nitro - benzyloxy-amine hydrochloride; m.p.: 210—215°C (under decomposition).

Example 20

Preparation of 3-aminoxymethyl-4-hydroxy-benzoic acid methyl ester

Method 1)

A mixture of 3.27 g. of 3 - (N - phthalimidooxymethyl) - 4 - hydroxybenzoic acid methyl ester and 1.71 g. of cyclopropylamine is heated at 60°C for 20 minutes. The residue is triturated with 25 ml. of 1 N hydrochloric acid. The phthalic acid N,N′ - dicyclopropylamide, which is insoluble in the acid, is filtered off and dried (yield: 2.32 g./95%/). The acidic filtrate is neutralized to pH=7.0 with solid potassium hydrogen carbonate, and the separated precipitate is filtered off and dried. 1.8 g. (91.5%) of 3 - aminoxymethyl - 4 - hydroxy - benzoic acid methyl ester are obtained; m.p.: 146—149°C (under decomposition).

Method 2)

3.27 g. of 3 - (N - phthalimidooxymethyl) - 4 - hydroxy - benzoic acid methyl ester are reacted as described in Example 1 to yield 1.7 g. (87%) of 3 - aminoxymethyl - 4 - hydroxy - benzoic acid methyl ester; m.p.: 147—149°C (under decomposition).

Example 21

Preparation of 3,4 - dichloro - benzyloxy-amine

3.22 g. of N - (3,4 - dichloro - benzyloxy) - phthalimide are reacted as described in Example 8, Method 2) to yield 2.0 g. (88%) of 3,4 - dichloro - benzyloxyamine hydrochloride, m.p.: 196—197°C.

Example 22

Preparation of 3,4-dimethoxy-benzyloxy-amine

6.26 g. of N - (3,4 - dimethoxy - benzyloxy) - phthalimide are reacted as described in Example 8, Method 3) to yield 3.7 g. (84%) of 3,4 - dimethoxy - benzyloxy-amine hydrochloride, m.p.: 152—153°C.

Example 23

Preparation of 1-(3-nitro-4-hydroxy-phenyl)-ethyloxyamine

1.97 g. of N - [1 - (3 - nitro - 4 - hydroxy - phenyl) - ethoxy] - phthalimide are reacted as described in Example 1 to yield 1.07 g. (73.4%) of 1 - (3 - nitro - 4 - hydroxy - phenyl) - ethyloxyamine

hydrochloride; m.p.: 203—206°C (under decomposition).

Example 24

Preparation of 3,4,5-trimethoxy-benzyloxy-amine

3.44 g. of N - (3,4,5 - trimethoxy - benzyloxy) - phthalimide are reacted as described in Example 17 to yield 2.0 g. (80%) of 3,4,5 - trimethoxy - benzyloxyamine hydrochloride; m.p.: 185—186°C.

Example 25

Preparation of 3-nitro-4-hydroxy-5-methoxy-benzyloxyamine

4.1 g. of N - (3 - nitro - 4 - hydroxy - 5 - methoxy - benzyloxy) - phthalimide are reacted as described in Example 2, step "B" to yield 1.66 g. (69%) of 3 - nitro - 4 - hydroxy - 5 - methoxy - benzyloxyamine hydrochloride; m.p.: 231—234°C (under decomposition).

Example 26

Preparation of 4-methoxy-3,5-dichloro-benzyloxyamine

3.53 g. of N - (4 - methoxy - 3,5 - dichloro - benzyloxy) - phthalimide are reacted as described in Example 8, method 4) to yield 2.26 g (87%) of 4 - methoxy - 3,5 - dichloro - benzyloxyamine hydrochloride; m.p.: 195—197°C.

Example 27

Preparation of 4-n-octyloxy-3,5-dimethoxy-benzyloxyamine

Step "A":

8.6 g. of 4 - n - octyloxy - 3,5 - dimethoxy - benzylbromide are reacted as described in Example 2, step "A" to yield 8.0 g. (75.5%) of N - (4 - n - octyloxy - 3,5 - dimethoxy - benzyloxy) - phthalimide; m.p.: 105—107°C.

Step "B":

4.44 g. of the above product are reacted as described in Example 1 to yield 3.12 g. (69%) of 4 - n - octyloxy - 3,5 - dimethoxy - benzyloxyamine tartrate; m.p.: 65—67°C.

Example 28

Preparation of 3-aminoxymethyl-4-hydroxy-5-nitrobenzoic acid methyl ester

3.72 g. of 3 - (N - phthalimidooxymethyl) - 4 - hydroxy - 5 - nitrobenzoic acid methyl ester are reacted as described in Example 1 to yield 2.4 g. (86%) of 3 - aminoxymethyl - 4 - hydroxy - 5 - nitrobenzoic acid methyl ester in the form of its hydrochloride. The compound melts at 195—201°C under decomposition.

Example 29

Preparation of 3-aminoxymethyl-4,5-dihydroxy-benzoic acid methyl ester

3.43 g. of 3 - (N - phthalimidooxymethyl) - 4,5 - dihydroxy - benzoic acid methyl ester are reacted as described in Example 1 to yield 2.36 g. (65%) of 3-aminoxymethyl-4,5 - dihydroxy - benzoic acid methyl ester tartrate; m.p.: 65°C (under decomposition).

Example 30

Preparation of 3 - aminoxymethyl-4-hydroxy-benzoic acid N,N-diethylamide

3.68 g. of 3 - (N - phthalimidooxy - methyl) - 4 - hydroxy - benzoic acid N,N - diethylamide are reacted as described in Example 1 to yield 1.97 g (51%) of 3 - aminoxymethyl - 4 - hydroxy - benzoic acid N,N - diethylamine tartrate. The highly hygroscopic salt decomposes at 35°C.

Example 31

Preparation of 3-aminoxymethyl-pyridine

Method 1)

A mixture of 2.54 g. of 3 - (N - phthalimidooxymethyl) - pyridine and 0.57 g. of cyclopyropylamine is heated at 60°C for 20 minutes. The mixture is deprived of the amine in vacuo over phosphorus pentoxide. The product is triturated with 25 ml. of 1 N hydrochloric acid, the insoluble cyclopropyl - phthalimide (1.6 g./85%/, m.p.: 134—136°C) is filtered off and dried. The acidic filtrate is evaporated under mild conditions, and the residue is triturated with a few ethanol and filtered. 1.42 g. (72%) of 3 - aminoxymethyl - pyridine hydrochloride are obtained; m.p.: 180°C (under decomposition).

Method 2)

2.54 g. of 3 - N - phthalimidooxymethyl) - pyridine are reacted as described in Example 3 to yield 1.8 g. (91%) of 3 - aminoxymethyl - pyridine hydrochloride; m.p.: 180—182°C (under decomposition).

Method 3)

2.54 g. of 3 - (N - phthalimidooxymethyl) - pyridine are reacted as described in Example 1 to yield 1.65 g. (84%) of 3 - aminoxy - methyl - pyridine hydrochloride; m.p.: 180°C (under decomposition).

Example 32

Preparation of 4-aminoxymethyl-pyridine

2.54 g. of 4 - (N - phthalimidooxymethyl) - pyridine are reacted as described in Example 1 to yield 1.6 g. (83%) of 4 - aminoxymethyl - pyridine hydrochloride; m.p.: 196—200°C (under decomposition).

Example 33

Preparation of 2-aminoxymethyl-pyridine

2.54 g. of 2 - (N - phthalimidooxymethyl) - pyridine are reacted as described in Example 1 to yield 1.65 g. (84%) of 2 - aminoxymethyl - pyridine hydrochloride; m.p.: 171—175°C.

Example 34

Preparation of 1-(pyridyl-3)-ethyloxyamine

Step "A":

8.9 g. of 1 - (pyridyl - 3) - ethylchloride are reacted as described in Example 2, step "A" to yield 10.5 g. (78%) of N - [1 - (pyridyl - 3) - ethoxy] - phthalimide; m.p.: 102—105°C.

Step "B":

2.68 g. of the above product are reacted as described in Example 1 to yield 1.53 g. (72.5%) of 1 - (pyridyl - 3) - ethyloxyamine hydrochloride; m.p.: 159—162°C (under decomposition).

Example 35

Preparation of 5-aminoxymethyl-imidazole

2.43 g. of 5 - (N - phthalimidooxymethyl) - imidazole are reacted as described in Example 2, step "B" to yield 0.9 g. (61%) of 5 - aminoxymethyl - imidazole hydrochloride.

Example 36

Preparation of 1-methyl-2-aminoxymethyl-benzimidazole

6.14 g. 1 - methyl - 2 - (N - phthalimido-oxymethyl) - benzimidazole are reacted as described in Example 1 to yield 4.1 g. (82%) of 1 - methyl - 2 - aminoxymethyl - benzimidazole hydrochloride; m.p.: 127—128°C (under decomposition).

Example 37

Preparation of 2-aminoxymethyl-benzthiazole

3.1 g. of 2 - (N - phthalimidooxymethyl) - benzthiazole are reacted as described in Example 1 to yield 1.8 g. (87.5%) of 2 - aminoxymethyl - benzthiazole hydrochloride; m.p.: 137—140°C (under decomposition).

WHAT WE CLAIM IS:—

1. A process for the preparation of substituted methoxyamines of general formula:

$$R^1CH(R^2)ONH_2$$

or salts thereof, in which R^1 is an aliphatic, aromatic or heterocyclic radical and R^2 is a hydrogen atom or a saturated or unsaturated straight-chain or branched C_{1-4} alkyl group, by reacting an N - (substituted methoxy) - phthalimide of general formula:

$$R^1CH(R^2)ON=A$$

in which A is a substituted or unsubstituted phthaloyl group and R^1 and R^2 have the same meanings as above, with an amine of general formula R^3NH_2 or with a salt thereof, in which R^3 is a hydrogen atom or an aliphatic, aromatic, araliphatic, alicyclic or heterocyclic radical, and optionally reacting the obtained base with an acid to produce a salt or reacting the obtained salt with a strong base to produce the free base.

2. A process according to claim 1 for the preparation of a salt of an alkoxy amine, in which said amine is an aliphatic amine and equimolar amounts of said aliphatic amine and said N - (substituted methoxy) - phthalimide are used.

3. A process according to claim 1, carried out in aliphatic alcohol containing from 1 to 3 carbon atoms, at the boiling point of the alcohol.

4. A process according to claim 1, in which the reaction of said N - (substituted methoxy) - phthalimide and said amine is carried out in the absence of any solvent, said N - substituted methoxy) - phthalimide and said amine being fused together at the boiling point of said amine.

5. A process according to any one of the preceding claims, in which said amine is n-butylamine, allylamine, cyclopropylamine, cyclohexylamine or aniline.

6. A process according to claim 1, in which said amine is ammonia in the form of an aqueous alcoholic solution.

7. A process according to any one of the preceding claims, in which said phthalimide is N - crotyloxy - phthalimide.

8. A process according to any one of claims 1 to 6, in which said phthalimide is N - (4 - n - octyloxy - 3,5 - dimethoxy - benzyloxy) - phthalimide.

9. A process according to any one of claims 1 to 6, in which said phthalimide is 4 - [1 - (pyridyl - 3) - ethoxy] - phthalimide.

10. A process according to claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

11. A substituted methoxyamine when produced by a process according to any one of the preceding claims.

12. Substitued methoxyamines of general formula:

$$R^1CH(R^2)ONH_2$$

in which R^1 represents a prop - 1 - enyl, 4 - n - octyloxy - 3,5 - dimethoxyphenyl, or 3 - pyridylmethyl group, and R^2 is a hydrogen atom or a saturated or unsaturated, straight-chain or branched C_{1-4} alkyl group.

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